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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 29985	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/SI03/00009	International filing date (day/month/year) 17.03.2003	Priority date (day/month/year) 26.03.2002
International Patent Classification (IPC) or both national classification and IPC C07D309/10		
Applicant KRKA TOVARNA ZDRAVIL, D.D., NOVO MESTO		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 07.10.2003	Date of completion of this report 21.11.2003
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bakboord, J Telephone No. +49 89 2399-2168



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/SI03/00009**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-12 as originally filed

Claims, Numbers

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/SI03/00009**

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	
Inventive step (IS)	Yes: Claims	1-12
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-12
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/SI03/00009

V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 The present invention relates to the desilylation of 4-silyloxytetrahydropyran-2-ones using triethylamine trihydrofluoride.

V.2 Reference is made to the following documents:

D1: EP-A-0349063, cited in the application

D2: EP-A-0331240, cited in the application

D3: WO-A-0046217, cited in the application

D4: WO-A-0145484, cited in the application

D5: PICQ D ET AL: 'UTILISATION DU COMPLEXE TRIETHYLAMINE-ACIDE FLUORHYDRIQUE POUR LA SYNTHÈSE DE DESOXYFLUOROPYRANOSIDES ET LA SCISSION DE GROUPES SILYLES SUBSTITUES', Carbohydrate Research (1987), 166, 309-313, cited in the application

D6: HAUFER G: 'TRIETHYLAMINE TRISHYDROFLUORIDE IN SYNTHESIS', Journal Für Praktische Chemie Chemiker-zeitung (1996), 338, 99-113, cited in the application

V.3 Novelty

Document D1 discloses the desilylation of 4-silyloxytetrahydropyrans using tetrabutylammoniumfluoride and acetic acid (claim 7).

Document D2 discloses the desilylation of 4-silyloxytetrahydropyrans using HF in acetonitrile (Scheme 1, p11, line 4-45 and p14, line 29-40).

Document D3 discloses the desilylation of 4-silyloxytetrahydropyrans using ammonium fluoride or ammonium hydrogen difluoride (claim 1). Document D3 also discloses tert-butyldimethylsilyloxy simvastatin as a crude product (examples 1-3).

Document D4 discloses the desilylation of 4-silyloxytetrahydropyrans using concentrated HCl in THF/1,4-dioxane (page 16, line 8-12). Document D4 also discloses tert-butyldimethylsilyloxy simvastatin as an oily compound (page 13, line

8-11).

Document D5 discloses that triethylamine trihydrofluoride can be used to remove a silyl protecting group from a primary alcohol under neutral conditions (p311, 2nd paragraph).

Document D6 discloses the use of triethylamine trihydrofluoride for the deprotection of silyl ethers (p99 and p111).

A process for the desilylation of 4-silyloxytetrahydropyrans using **triethylamine trihydrofluoride** is disclosed in none of the documents. Claims 1-10 therefore fulfill the requirements of Art 33(2) PCT.

Tert-butyldimethylsilyloxy simvastatin in a solid form is disclosed in none of the documents. Claim 11 therefore fulfills the requirements of Art 33(2) PCT.

Claim 12 describes the use of tert-butyldimethylsilyloxy simvastatin in a solid form and is novel by consequence.

V.4 Inventive step

Starting from documents D1-D4 the problem to be solved by the present application may be regarded as how to provide a novel possibly improved process for the desilylation of 4-silyloxytetrahydropyrans. The solution of the applicant resides in the use of triethylamine trihydrofluoride and the use of purified solid tert-butyldimethylsilyloxy simvastatin. The applicant shows in examples 1-3 and the reference examples 1 and 2 that the process of the present application results in solid simvastatin in an adequate purity. Compared to the processes of the prior art where the yield is either lower or simvastatin is obtained as an oil this is an improvement. As the use of triethylamine trihydrofluoride for the desilylation of 4-silyloxytetrahydropyrans has not been made obvious by the prior art the solution of the applicant may be regarded as involving an inventive step (Art 33(3) PCT).